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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/751,962	12/29/2000	David E. Catcheside	10552.13USC1	2958
23552	7590	06/01/2004	EXAMINER	
MERCHANT & GOULD PC			LAMBERTSON, DAVID A	
P.O. BOX 2903			ART UNIT	
MINNEAPOLIS, MN 55402-0903			PAPER NUMBER	
1636				

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/751,962	CATCHESIDE, DAVID E.	
	Examiner David A. Lambertson	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 26 February 2004.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-69 and 128-140 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-3,8-36,42-69,129-131,133,134 and 136-140 is/are rejected.
- 7) Claim(s) 4-7,37-41,128,132 and 135 is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 26, 2004 has been entered.

Claims 1-69 and 128-140 are pending and under consideration in the instant application. Claims 70-127 were cancelled by Applicant in the response filed August 26, 2002. Claims 128-140 are newly added. Any rejection of record in the previous Office Action, mailed August 26, 2003, that is not addressed in this action has been withdrawn.

Acknowledgement is made of Applicant's declaration under 37 CFR § 1.132.

Miscellaneous

Applicant requested clarification with regard to the objection of claims 4-7 and 37-41 in the previous Office Action. In response, it is submitted that the claims were properly objected to because they were dependent on rejected claims, and therefore not allowable. The Office asserts that the record is now clear with regard to the proper status of claims 4-7 and 37-41.

Claim Objections

Claims 133, 135 and 136 are objected to because of the following informalities: the claims appear to contain several spelling errors. Specifically, claim 133 recites "Aspersellins"

which appears to be a misnomer of *Aspergillus*; claim 135 recites “*Saccharomyces cerevisiae*” which appears to be a misnomer of *Saccharomyces cerevisiae*; and claim 136 recites “*Mus muscles*” which appears to be a misnomer of *Mus musculus*. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 8-36, 42-69, 133 and 134 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for the reasons set forth in the previous Office Action, and is now applied to newly added claims 133 and 134.**

Response to Arguments Concerning Claim Rejections - 35 USC § 112

Applicant's arguments filed February 26, 2004 have been fully considered but they are not persuasive. Applicant provides the following grounds of traversal with regard to the instant rejection:

1. The declaration indicates that “[I]t is generally known that there are only about sixty (60) types of eukaryotes” (see for example the declaration, section 5) as opposed to the “huge number of species suggested by the Examiner” (see for example Applicant’s arguments, page 13, second

paragraph), and that based on the disclosure of at least 24 different hotspots in the specification, more than a representative number of species of eukaryotic recombinational hotspots have been described. It is asserted that, based on this representative number of species, the Written Description requirement has been satisfied.

2. It is asserted that the claimed invention is not directed to eukaryotic recombinational hotspots, *per se*, but rather to a method of employing these hotspots (see for example section 7 of the declaration).

3. The declaration further states that the application provides a complete and thorough description of an “inventive method for diversifying genes using eukaryotic hotspots,” wherein other researchers, after reading and understanding the specification, could then find and use newly discovered hotspots in the invention (see section 8 of the declaration, especially the final two lines of the section).

4. It is finally argued that, although the Examiner suggests a disclosure of a structure-function relationship for eukaryotic recombinational hotspots is necessary, eukaryotic recombinational hotspots are not properly tied to structure. It is further stated that a eukaryotic recombinational hotspot can only be defined by its function (see for example page 13, third paragraph of Applicant’s Remarks).

Applicant’s arguments have been fully considered but are not found convincing for the following reasons:

1. First, the Office interprets the term “types” as set forth in section 5 of the declaration to be synonymous with “species.” This is based upon the attached definition by Merriam-Webster of

the term "type," which in section 1 of the definition refers to "types" in a taxonomic sense as "species" (see for example the last sentence in part 1 of the definition). Based on this definition, the Office stringently disagrees with the assertion that it is generally accepted that there are only 60 different types of eukaryotes. Eukaryotes are made up of 4 individual Kingdoms: Animal, Fungi, Plant and Protists. Each of these Kingdoms has many thousands of species of eukaryotic organisms, each of which will have unique recombination hotspots. For example, Mammalia is a particular class within a particular phylum of the Animal Kingdom. As evidenced by the attached web site directory to the Department of Systemic Biology: Vertebrate Zoology page maintained by the Smithsonian Institute, there are almost 5,000 species of mammals alone. Take into consideration the number of Protists, Plants, Non-Mammalian Animals (such as Invertebrates and Avians), and Fungi, and there are an immense number of eukaryotes. The disclosure of 24 recombinational hotspots, 16 of which come from two distinct organisms (8 from *S. cerevisiae* and 8 from *N. crassa*), does not adequately describe the broad genus of recombinational that are an essential functional feature of the instantly claimed product. The specification does describe those specific recombinational hotspots that have not been rejected in the instant claims; however, this does not allow the skilled artisan to envision all eukaryotic recombinational hotspots because there is no structure-function relationship for such hotspots (see also the arguments presented below). Furthermore, the disclosure of this small number of recombinational sequences, many of which come from select organisms, does not represent the broad genus of eukaryotic recombinational hotspots that are a necessary functional feature of the claimed product.

2. The claimed invention is not directed to a method, as asserted in the declaration. Rather, the claims are directed to products (i.e., haploid or diploid fungal cells), where the necessary functional limitation of the cells that allegedly distinguishes it from the prior art is the presence of a eukaryotic recombination hotspot that is functionally coupled to a heterologous recombinant genome. In order to envision such cells, the skilled artisan would absolutely need to be apprised of what eukaryotic recombination hotspots were usable in the cells, and which recombinase proteins were required to act upon the sequences thus causing a recombination event. However, as stated above, there is a largely unknown body of eukaryotic recombinational hotspots within the broad genus that is claimed, and which are not described in either the instant specification or the prior art. Coupled with the fact that there is no discernible structure-function relationship for eukaryotic recombination hotspot sequences, the skilled artisan could not ascertain the broad genus of eukaryotic recombination hotspot sequences that can functionally describe the claimed invention.

3. It is again noted that the claimed invention is to a product, and not to a method as again set forth in this argument. This is an important distinction, especially with regard to the statement that other researchers, after reading and understanding the specification, could then find and use newly discovered hotspots in the invention; this is tantamount to an invitation to experiment. This statement indicates that products that have not and cannot be envisioned are being claimed in the instant invention. If researchers have yet to identify the eukaryotic recombinational hotspots that can be put into the claimed fungal cells, one cannot envision the fungal cells that contain these unknown eukaryotic recombinational hotspot sequences. The fact of the matter is that the instant claims are directed to products that are claimed to contain an as of yet

unidentified component that is functionally pertinent to the claimed invention. If the necessary functional element of the product is unknown, the product as claimed cannot be described.

4. The fact that recombinational hotspots are not properly tied to a structure-function relationship is exactly the reason why the Written Description requirement has not been achieved. If there were a structure-function relationship between eukaryotic recombinational hotspots, the skilled artisan would be able to envision other functionally relevant eukaryotic recombination hotspots that can be placed in the claimed invention. However, as acknowledged by the arguments set forth in the response, there is no such relationship, and eukaryotic recombinational hotspots must be identified in an empirical fashion, on an individual basis. This fact, coupled with the immense number of eukaryotic cells (each of which will have their own unique recombination hotspots) in comparison to the small number of known eukaryotic recombinational hotspots, dictates that the skilled artisan cannot envision the functional element of the claimed products, and therefore cannot envision the claimed products themselves.

In conclusion, it is reiterated that there are a vast number of eukaryotes, each of which has unique recombinational hotspots. Eukaryotic recombinational hotspots are only known in a few organisms, and it is unclear that these are comprehensive with respect to the organism. This statement is exemplified in the instant claims, which broadly and vaguely claim limitations, such as a eukaryotic hotspot that exists in *Aspergillus* or *Schizophyllum commune* (see for example claims 133 and 134) without a clear indication of the location or sequence nature for these functional elements. It is also stressed that the claims are directed to products and not methods, as seemingly thought in view of statements made in the declaration. This is an important point

because the product must be “envisioned” by the skilled artisan in order to meet the Written Description requirement. Applicant recognizes that there are eukaryotic recombinational hotspots that have not yet been identified (e.g., section 3 as set forth above), but persists in claiming products that comprise these sequences. Clearly, these products cannot be envisioned if the sequences that are the functional element of the products are completely unknown. This is accentuated by the recognition that there is no structure-function relationship between eukaryotic recombination hotspots, making it impossible to envision (i.e., predict) which sequences from the hundreds of thousands of other eukaryotes would be functional in the claimed products. As a result, the rejection under 35 USC § 112, first paragraph, Written Description, must be maintained.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 129-131 and 136-140 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection that is necessitated by amendment of the claims.**

Claim 129 indicates that the recombination hotspot is *N. crassa nut-2*. This claim is indefinite because there does not appear to be a recombinational hotspot for a gene *nut-2*. It is noted that the specification describes a recombinational hotspot for the *nit-2* gene, but it remains unclear if this is the desired limitation of the claim. It would be remedial to appropriately

indicate the name of the gene that houses the recombinational hotspot, be it *nit-2* or some other gene.

The term "near" in claims 130, 131, 136 (the term "close to" is interpreted to be equivalent to the term "near") and 137-140 is a relative term which renders the claim indefinite. The term "near/close to" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably aware of the scope of the invention. Specifically, it is unclear if the term "near/close to" is meant to indicate a level of proximity between the indicated genes and the recombination hotspot, or if it is meant to indicate a level of sequence homology between the hotspot and either the native sequence of the hotspot or the sequence of the gene itself. Additionally, if the term is meant to indicate proximity, it is unclear how near this sequence must be in order to meet the boundaries of the limitation; if the term is meant to indicate level of sequence homology, it is unclear what level of homology is acceptable to meet the boundaries of the limitation.

Claims 139 and 140 recite a range of limitations without a clear delineation between the two limitations. Specifically, claim 139 indicates that the recombinational hotspot is "near a gamma globular 10ci in *Homo sapiens* is in the region of the repeat sequences associated with Charcot-Marie-Tooth neuropathy in *Homo sapiens*." It is not immediately clear if the hotspot is to be either of these seemingly mutually exclusive hotspots, if it is a combination of the hotspots, or if it is an *H. sapiens* 10ci hotspot that is also found in the repeat sequences associated with Charcot-Marie-Tooth neuropathy. A similar situation exists with claim 140, concerning the 10ci hotspot and the retinoic acid alpha receptor.

Allowable Subject Matter

No claims are allowed.

Claims 4-7, 37-41, 128, 132 and 135 are objected to as being dependent upon a rejected base claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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